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(54) Title: USE OF XENON FOR TREATING NEUROINTOXICATIONS

(57) Abstract

The present invention relates to the use of xenon or xenon gas mixtures for treating neurointoxications. In particular, the present invention is directed to such a xenon use in which the neurointoxication is caused by a neurotransmitter excess. Xenon can reduce the release of neurotransmitters, particularly dopamine, which are caused e.g. by hypoxic situations such as an apoplexy or a craniocerebral trauma. A preparation containing xenon can also be used as therapeutic agent in the case of depressions, schizophrenia and Parkinson's disease, in which the neurotransmitter equilibrium is also disturbed. The application by inhalation is simple and the harmlessness of xenon has already been proved by its use as anesthetic agent.

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Use of Xenon for Treating Neurointoxications

The present invention relates to the use of xenon for treating neurointoxications. In particular, the present invention relates to a use of xenon in which the neurointoxication is caused by a neurotransmitter excess.

The uncontrolled release of neurotransmitters, particularly glutamate, noradrenalin and dopamine, is responsible for many acute and chronic intoxications of the brain, what is called neurointoxications or neuropoisonings. These neurotransmitters kill the affected neurons either by induction of apoptosis (controlled cell death) and/or secondary by their metabolites by forming oxygen radicals which in turn have toxic effects. An uncontrolled release of neurotransmitters which result in a strongly increased concentration of the neurotoxins in the affected tissue, can be due to various endogenous or exogenous causes. For example, an increased release of glutamate or dopamine may result in an acute craniocerebral trauma. An increase in the neurotransmitter release has also been observed as a response to oxygen deficiency in the brain, e.g. in the case of apoplexy (ischemia) or in the case of other hypoxias, particularly during the child birth. Drug abuse represents another cause of impaired neurotransmitter release. In certain forms of schizophrenia, stress-induced relapses back into schizophrenia (acute episodes) are also accompanied by increased neurotransmitter release. Finally, a chronic shift of neurotransmitter balance, particularly of dopamine balance, has also been observed in various regions of the brain in the case of Parkinson's disease. Increased dopamine release and subsequent formation of free radicals occur here as well. Various investigations made with cell cultures and experimental animals prove the release of neurotransmitters, particularly as a result of oxygen deficiency.

For example, it could be shown that in rats into which the dopamine neurotoxin 6-hydroxy-dopamine was infused unilaterally into the substantia nigra, which resulted in a unilateral depletion of dopamine in the ipsilateral striatum, an experimentally induced ischemia in the regions of dopamine depletion led to a damage which was less than that in other regions of the brain. These results suggest that dopamine plays a part in ischemia-induced striatal cell death (Clemens and Phebus, Life Science, Vol. 42, p. 707 et seq., 1988).

It could also be shown that dopamine is released in great amounts from the striatum during cerebral ischemia (Kahn et al., Anest.-Analg., Vol. 80, p. 1116 et seq., 1995).

The release of neurotransmitters during cerebral ischemia was investigated in detail and seems to play a key role for excitotoxic neural death. For example, Kondoh et al., Neurosurgery, Vol. 35, p. 278 et seq., 1994, showed that changes in the neurotransmitter release and metabolization can reflect changes in the cellular metabolism during an ischemia. The increase in the extracellular dopamine concentration in the striatum of experimental animals in which experimental apoplexies were induced, is well documented.

The contribution of excess dopamine to neuronal damage can be derived from the ability of dopamine antagonists to obtain protection of the neurons in ischemia models (Werling et al., Brain Research, Vol. 606, p. 99 et seq., 1993). In a cell culture, dopamine causes primarily apoptosis of striatal neurons without damaging the cells by a negative effect on the oxidative phosphorylation (ATP/ADP ratio remained unchanged). However, if its effect is combined with a minimum inhibition of mitochondrial functions, the neurotoxic effect of dopamine will be increased significantly (McLaughlin et al., Journal of Neurochemistry, Vol. 70, p. 2406 et seq., 1998).

In addition to the direct hypoxic toxicity on neurons, the stress induced by oxygen deficiency effects, particularly during a birth, an increased dopamine release which results in a negative conditioning of the brain for dopaminergic regulations. This means that even children who seem to survive a hypoxic birth phase uninjured, have a tendency preferably towards convulsions and epileptic conditions when they are older.

Another cause of a disturbed neurotransmitter release is represented by drug abuse. In particular if drugs such as designer drugs (e.g. ecstasy, etc.) or heroin are consumed and amphetamines are overdosed, the persons will show signs of intoxication and often spasmophilia which is based on an increased neurotransmitter release.

The causes of schizophrenia are also due to a complex impairment of the neurotransmitter regulation. Schizophrenia patients are often asymptomatic over a prolonged period of time but they have a tendency towards spontaneous schizophrenia attacks which are obviously triggered by a stress-induced dopamine release even in minor stress situations. Here, one speaks of catatonic schizophrenia. Further neuropsychiatric diseases which are based on an increased neurotransmitter release are depressions and Gilles de la Tourette syndrome ("maladie de tics", "Tics impulsif").

Finally, one cause of Parkinson's disease is seen today in the dopamine modulation and in the dopamine metabolism. In Parkinson's disease, dopaminergic neurons in the striatum are especially damaged. References exist to the effect that Parkinson's disease is caused by a dopamine excess in the affected region of the posterolateral hypothalamus and the substantia nigra. Many neurons are found in this region, which have lost their functionality but not their vitality. These neurons referred to as "orphan neurons" release continuously neurotransmitter amounts having pathologic effects.

With the exception of Parkinson's disease where dopa precursors are used as preparations and basically of schizophrenia, no therapeutic approaches exist so far which focus on a reduction of the dopamine concentration in the environment of endangered cells.

Therefore, there is a demand for a preparation which reduces or prevents the damaging effect of uncontrolled neurotransmitter release, e.g. of dopamine, glutamate or noradrenalin, from neurons. It is the object of the present invention to provide such a preparation which can be of use in the above-mentioned and in further fields of application.

This object is achieved by the subject matters defined in independent claims 1, 15 and 17. Further advantageous embodiments and aspects of the present invention follow from the dependent claims, the description and the attached drawing.

It has been found that the noble gas xenon surprisingly suppresses reversibly the release of neurotransmitters, particularly dopamine and glutamate. This unexpected discovery opened up the possibility of producing preparations for treating cell damage and diseases, respectively, which are caused by an increased neurotransmitter release, particularly dopamine release or glutamate release.

Correspondingly, the present invention generally focuses on the use of xenon for treating neurointoxications and on the production of a preparation containing xenon for treating neurointoxications, respectively. The invention also relates to the preparation as such and to a method of producing the same. Such neurointoxications concern particularly a neurotransmitter excess. The invention is based particularly on the insight that xenon reduces the release of dopamine and/or glutamate.

According to the invention neurointoxications are understood to mean acute or chronic "states of poisoning" of the CNS, particularly of the brain, which in most cases result in severe deficiency symptoms of the affected areas. These states of poisoning result from a neurotransmitter excess, particularly of glutamate, noradrenalin and/or dopamine, which can be due to a variety of causes. The above-mentioned diseases, such as apoplexy, hypoxias, oxygen deficiency during a birth, Parkinson's disease, craniocerebral trauma, drug abuse, schizophrenia, depressions and Gilles de la Tourette syndrome have to be mentioned here. The inventors also found that patients who must be connected to a cardio-pulmonary bypass machine often suffer from cerebral deficiency symptoms which are due to a neurotransmitter excess caused by hypoxia. For example, the use of the cardio-pulmonary bypass machine can cause an often unidentified neurointoxication which delays the patient's reconvalecence considerably. It was also found that any prolonged artificial respiration can result in an undesired neurointoxication as side-effect. In recent investigations conducted by the inventors, the surprising insight was gained that the hearing loss (e.g. due to noise, presbycusis, tinnitus, sudden deafness) can also be caused by a neurointoxication. The excess neurotransmitter release, particularly excessive glutamate and dopamine release which can have been caused e.g. by an impairment in the body, an acoustic trauma or an ischemia, results in an acute destruction of the nerve endings and subsequently death of the corresponding nerves in the organs of hearing. Migraine has to be considered another disease which is most likely due to an impaired dopamine balance and thus to a neurointoxication.

The discovery that the neurotransmitter release can be influenced by xenon enables a fully new field of application for this noble gas, which has been used increasingly as inhalation anesthetic agent in the anesthetic field so far. The treatment of the differing, above-mentioned and other neurotransmitter excess diseases of the brain can be carried

out on the basis of the present invention by a simple inhalation therapy. The uptake of xenon via the respiratory system and the transport into the brain are already proved by the use as anesthetic agent. It can also be assumed that the use of xenon has no damaging effect on the human organism, since many corresponding experiences could be made already by its use as anesthetic agent. Xenon can be applied by various techniques which can be chosen as a function of the location of use. For example, inhaling apparatus can be used in the clinics, which are also used for anesthesia by inhalation. If a cardio-pulmonary bypass machine or other artificial breathing apparatus is used, xenon can be added directly in the machine and requires no further apparatus. Here, the standard xenon addition can prevent the formation of neurointoxications in the model case (prophylaxis) or at least reduce the deficiency symptoms. On an ambulant basis, e.g. in the primary treatment of victims of an accident, it is possible to use simpler inhalators which mix the xenon with the ambient air during the process of inhalation. In this connection, it is also possible to adapt the xenon concentration and the timing of xenon use in simple manner to the therapeutic requirements. For example, it is advantageous to use mixtures of xenon with other gases, it being possible to mix the xenon with oxygen, nitrogen, air or other gases harmless for humans.

In patients suffering from a severe craniocerebral trauma, respiration with a xenon-oxygen mixture, as also used in anesthesia, can prevent, or at least reduce, the release of dopamine and thus the secondary neurotoxic effects accompanying this trauma. In such accidents, the additional anesthetic side-effect is desired, since the patient can be freed from pain by this.

An essential feature of acute ischemia in the brain is represented by the secondary neurotoxic effects which form by an increase in the neurotransmitter release and are responsible for the death of the neurons in the ischemic marginal region. Although an immediate xenon treatment, e.g.

still by the emergency physician who carries out the initial treatment in the case of an apoplexy patient, cannot prevent ischemia per se, it can at least reduce, or even prevent, the neurotoxicity by the secondarily released neurotransmitters. Thus, the permanent damage frequently occurring in the case of apoplexy can be reduced. The same applies analogously to measures which will have to be taken if disease symptoms occur after drug abuse and loss of hearing or a migraine attack.

In the case of oxygen deficiency during a birth, e.g. during the entrance into the obstetric canal or in the case of problems with the umbilical cord, xenon-(oxygen) respiration of the mother and respiration of the child as soon after the birth as possible, respectively, can prevent the negative effects of increased dopamine release during the oxygen deficiency.

In the case of schizophrenia patients suffer from periodic schizophrenia (catatonia), the progress is very sudden, the picture of the state being characterized by dramatic symptoms which show varying pictures and are full of delusions and hallucinations. Often a phase disappears as rapidly as it started. Such phases or attacks can be triggered spontaneously by stress situations. Rapid respiration with a xenon gas mixture during the state of stress can at least reduce the intensity of the attack. For this application it is an obvious thing to equip patients with xenon inhalators which permit self-medication. Here, it is conceivable to use containers which - similar to asthma sprays - are filled with xenon which will be released if a trigger is pressed. The same applies analogously to the treatment of depressive patients whose moods change almost daily and who as a result thereof require state-related medication.

The chronic Parkinson's disease is accompanied by progressive symtoms. A consequent xenon treatment here reduces the neurotransmitter release and slows down the

progression or even brings the progression of the disease to a stand-still. In this case, intermittent treatment offers itself in which the patient is respirated with xenon at certain intervals. The same applies to patients who suffer from the Gilles de la Tourette syndrome. Their tics also become more and more distinct as the disease proceeds.

In the case of acute threatening states, such as a craniocerebral trauma or an ischemia, the respiration can advantageously be carried out with a xenon-oxygen mixture of 90:10 % by volume, preferably 80:20 % by volume, most preferably 75-70:25-30 % by volume, over several hours to one day. As compared thereto, the intermittent respiration by a xenon-air mixture to which less xenon has been added, e.g. 5 to 30 % xenon, preferably 10 to 20 % xenon, can be considered in chronic progressions of a disease.

Various methods for the inhalation of xenon and xenon mixtures, respectively, can be used which depend on the respective intended use. In clinics, it is possible to use anesthetic apparatus, in which prefabricated xenon-oxygen mixtures can be connected to the corresponding inlets of the anesthetic apparatus. The respiration is then carried out according to a procedure common for such apparatus. The same applies analogously to the cardio-pulmonary bypass machine.

As an alternative, xenon can be mixed with ambient air instead of oxygen in the mobile use, which due to the smaller size of the required pressure bottles increases the mobility of the apparatus. For example, it is possible to use an inhalator which supplies xenon from a pressure bottle and is accommodated in a support together with the latter, to a mixing chamber. On one side, this mixing chamber contains a mouthpiece for inhaling the xenon and on the other side on which the xenon is supplied to the mixing chamber it has at least one additional check valve which enables the inlet of ambient air. The xenon pressure container can be equipped with a pressure reducing valve, for example, which reduces the amount of xenon gas supplied

to a suitable value. When the patient breathes in, he sucks in air from the air valves. In the mixing chamber, this air is mixed with the supplied xenon to the desired ratio and then inhaled by the patient. An advantageous inhalator intended for mobile use and serving for inhaling xenon and its mixtures is shown in EP-B-0 560 928, for example.

In a further simplified embodiment, e.g. for self-medication, a mouthpiece is connected directly to the xenon pressure container. During the inhalation the patient opens the pressure valve and inhales xenon simultaneously with the air from the environment. When he breathes out, he releases the valve, so that no more xenon reaches the mouthpiece. In this way, at least a coarse regulation of the amount of inhaled xenon is possible.

The invention is explained in more detail below, reference being made to attached figures 1 and 2, which show the dopamine release in cell cultures exposed to hypoxic shock.

The function of the invention shall be explained below by means of the following examples.

Example 1

An *in vitro* experiment with PC12 cells is concerned. These PC12 cells are dependants of a pheochromocytoma of rats. Here a catecholamine-producing tumor of the suprarenal cortex is concerned, which shows permanent dopamine release in a malignant form. PC12 cells can be reproduced continuously *in vitro*. Following the addition of "nerve growth factor", they start differentiating and become neurons which in many respects have the property of *in vivo* neurons, particularly the properties which relate to the neurotransmitter release. PC12 cells are acknowleded as neuronal model.

PC12 cells differentiated in such a way were exposed to a hypoxic situation whereupon they release dopamine. Such a hypoxic situation is an artificially induced stress state for the cells, in which e.g. the oxygen supply is dropped or impeded. If the cells are treated under these hypoxic conditions with xenon in defined concentrations over the same period of time, the neurotransmitter release will be dropped. The time course of such an experiment is shown in figure 1 by way of example. The curve of the non-stressed controls, illustrated by solid squares, shows a low dopamine concentration throughout the time course, which is subject to certain fluctuations. If a hypoxic situation is triggered by the dose of helium instead of oxygen, the curve of the dopamine concentration will result as shown in the curve with the solid triangles. A maximum dopamine concentration shows here after about 40 minutes. However, if xenon is given in a hypoxic situation, the cells will virtually no longer differ from the control cell population as shown by the plot illustrated by solid circles. In connection with the relative dopamine concentration shown in part B of figure 1 it can also clearly be seen that the dopamine release is reduced down to values of the control cells. In this connection, it was found that the xenon effect is fully reversible, so that the cells treated in this way cannot be distinguished from untreated cells after the xenon is washed out. In the above-described experiment, the gases used were given to the cells by mixing them with the growth buffer for the cells. Here, saturated gas buffer solutions are concerned each.

Example 2

The differentiated PC12 cells described in Example 1 were distributed to various vessels and exposed to differing conditions. The results are shown in figure 2.

Control: incubation in normal atmosphere (ambient air)

N_2: incubation in nitrogen (N_2) for 30 minutes [= hypoxia]

Xenon: incubation in xenon for 30 minutes

Glu: addition of 10 µM glutamate for 30 minutes of incubation in a normal atmosphere

Glu + N_2: addition of 10 µM glutamate for 30 minutes of incubation in N_2

Glu + Xe: addition of 10 µM glutamate for 30 minutes of incubation in xenon.

A hypoxic condition and an increased release of dopamine resulted in the cells incubated with nitrogen (group: N_2). The dopamine release could be even increased if in addition to the nitrogen atmosphere glutamate which represents a neurotransmitter and has a neurotoxic effect in greater doses was given as well (group: Glu + N_2). However, if 10 µM glutamate was given in the simultaneous presence of xenon (Group: Glu + Xe), a slightly increased dopamine release would still result but it was reduced by two thirds as compared to the corresponding (glutamate + N_2) experiment.

The results shown in figure 2 elucidate that in stress situations such as hypoxia, the neurotransmitters glutamate and dopamine are released in large quantities. This results in a) direct damage to the neighboring neuronal tissues, mainly by inducing apoptosis and b) indirectly, an additional increased release of other neurotransmitters. Thus, the addition of glutamate to the cells effects an increased dopamine release, particularly when the cells were kept under hypoxic conditions. The unintentional neurotransmitter release could be reduced many times over by the simultaneous supply of xenon.

All in all, it could be shown in the present invention that xenon can stop rapidly and without other permanent side-effects the neurotransmitter release temporarily. Hence it follows that xenon can be used in defined concentrations in a therapeutically useful manner in all pathologic conditions characterized by unregulated neurotransmitter release. The

simple application by inhalation and the harmlessness of xenon render this therapy especially attractive.

Claims

1. Use of xenon or xenon gas mixtures for treating neurointoxications.

2. Use according to claim 1, characterized in that the neurointoxication is caused by a neurotransmitter excess.

3. Use according to claim 1 or 2, characterized in that the xenon reduces the release of dopamine, glutamate and/or noradrenalin.

4. Use according to any one of claims 1 to 3, characterized in that the neurointoxication is caused by an apoplexy.

5. Use according to any one of claims 1 to 3, characterized in that the neurointoxication is caused by drug abuse.

6. Use according to any one of claims 1 to 3, characterized in that the neurointoxication is caused by oxygen deficiency during a birth.

7. Use according to any one of claims 1 to 3, characterized in that the neurointoxication is correlated with a Parkinson's disease, schizophrenia or Gilles de la Tourette syndrome.

8. Use according to any one of claims 1 to 3, characterized in that the neurointoxication is caused by a craniocerebral trauma.

9. Use according to any one of claims 1 to 3, characterized in that xenon or xenon gas mixture is used in a cardio-pulmonary bypass machine.

10. Use according to any one of claims 1 to 3, characterized in that the neurointoxication causes loss of hearing.

11. Use according to any one of claims 1 to 3, characterized in that the neurointoxication is caused by migraine.

12. Use according to any one of claims 1 to 10, characterized in that an administered preparation for therapy contains 5 to 90 % by volume of xenon.

13. Use according to claim 12, characterized in that the preparation contains 5 to 30 % by volume of xenon.

14. Use according to any one of claims 1 to 13, characterized in that an administered preparation for therapy further contains oxygen and/or nitrogen and/or air.

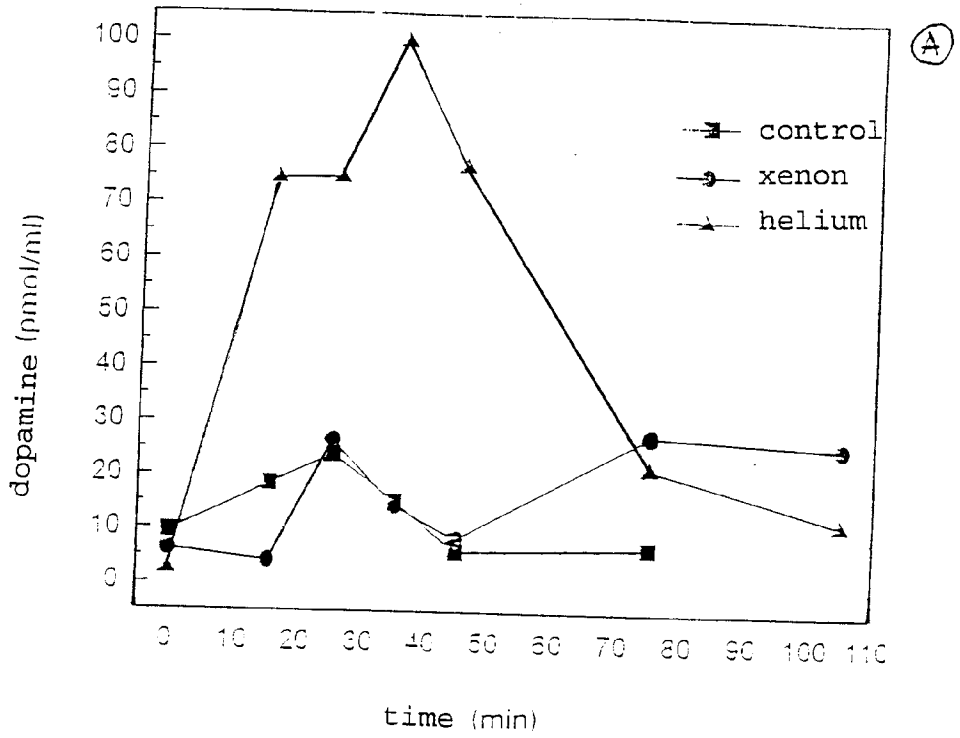
15. Use according to claim 12, characterized in that the preparation has a ratio of xenon to oxygen of 80 to 20 % by volume.

16. A preparation containing xenon or a xenon gas mixture for treating neurointoxications.

17. The preparation according to claim 13, containing xenon and an oxygen-containing gas.

18. A method of producing an inhalable preparation by mixing xenon with another gas harmless for humans.

19. The method according to claim 18, wherein xenon is mixed with an oxygen-containing gas.


A
control
xenon
helium
dopamine (pmol/ml)
time (min)

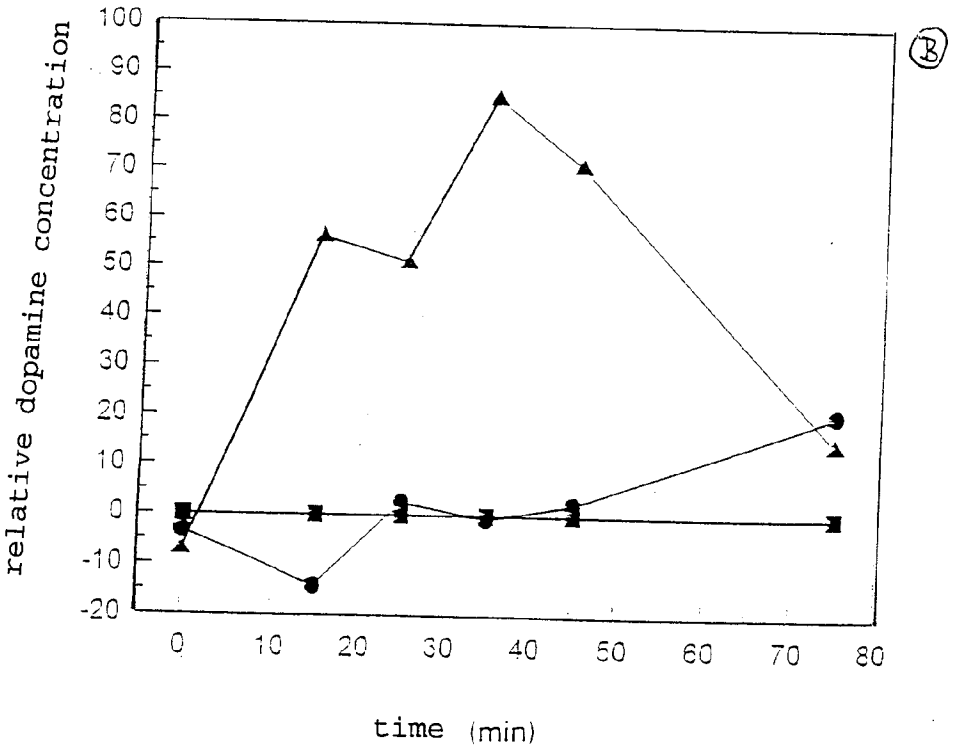
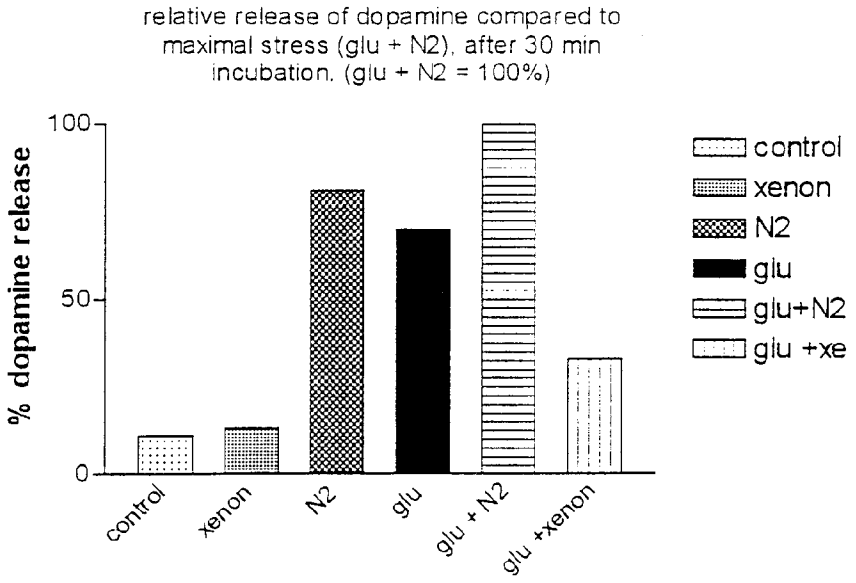

B
relative dopamine concentration
time (min)

Fig. 1

Figure 2


relative release of dopamine compared to maximal stress (glu + N2), after 30 min incubation. (glu + N2 = 100%)
% dopamine release
100
50
0
control
xenon
N2
glu
glu + N2
glu +xenon
control
xenon
N2
glu
glu+N2
glu +xe

INTERNATIONAL SEARCH REPORT

Ir. ational Application No
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A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K33/00 A61P25/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

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IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, PAJ, WPI Data, BIOSIS, CHEM ABS Data, EMBASE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 0 864 328 A (M.GEORGIEFF) 16 September 1998 (1998-09-16) claim 1 page 3, line 46-56	1
X	EP 0 864 329 A (M.GEORGIEFF) 16 September 1998 (1998-09-16) claims 1-6 page 3, column 45-51	1

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

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Date of the actual completion of the international search	Date of mailing of the international search report
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INTERNATIONAL SEARCH REPORT

Information on patent family members

In ational Application No
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